

Application No. 10/076,071
Amendment dated January 23, 2007
Reply to Office Action dated July 25, 2006

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-530 (Canceled).

531. (Currently amended) A method of treating an angiogenic disease or condition in an animal comprising administering to the animal an ~~effective~~ amount of a metal-binding peptide which does not have a metal ion bound to it or of a physiologically-acceptable salt of the peptide, the amount of the peptide or salt which is administered to the animal being effective to inhibit angiogenesis, the sequence of the peptide being:

$$P_1 - P_2,$$

wherein:

P_1 is:

Xaa₁ Xaa₂ His or

Xaa₁ Xaa₂ His Xaa₃,

the P_1 portion of the peptide being linear;

P_2 is (Xaa₄)_n;

Xaa₁ is the N-terminal amino acid of the peptide, the only substituents on the α -amino group of Xaa₁ are hydrogen, and Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

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n is 0-10;

~~or a physiologically-acceptable salt thereof.~~

532. (Previously presented) The method of Claim 531 wherein:

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, glutamic acid, lysine, hydroxylysine, histidine, arginine, or α -hydroxymethylserine, and

Xaa₂ is alanine, valine, leucine, isoleucine, threonine, serine, asparagine, glutamine, cysteine, methionine, lysine, hydroxylysine, histidine, arginine, or α -hydroxymethylserine.

533. (Previously presented) The method of Claim 531 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine or α -hydroxymethylserine.

534. (Previously presented) The method of Claim 531 wherein Xaa₂ is alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

535. (Previously presented) The method of Claim 531 wherein Xaa₃ is lysine.

536. (Previously presented) The method of Claim 531 wherein:

Xaa₁ is aspartic acid, glutamic acid, arginine, lysine, threonine, serine or α -hydroxymethylserine,

Xaa₂ is alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and

Xaa₃, when present, is lysine.

537. (Previously presented) The method of Claim 536 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, valine, leucine, isoleucine, threonine, serine or α -hydroxymethylserine.

538. (Previously presented) The method of Claim 537 wherein Xaa₂ is alanine, valine, leucine or isoleucine.

539. (Previously presented) The method of Claim 538 wherein P₁ is Asp Ala His or Asp Ala His Lys.

540. (Previously presented) The method of Claim 539 wherein P₁ is Asp Ala His Lys.

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541. (Previously presented) The method of Claim 536 wherein Xaa₁ is arginine, lysine, threonine, serine or α -hydroxymethylserine, and Xaa₂ is alanine, valine, leucine, isoleucine, threonine, serine or α -hydroxymethylserine.

542. (Previously presented) The method of Claim 541 wherein P₁ is Thr Leu His, HMS HMS His or Arg Thr His.

543. (Cancelled)

544. (Previously presented) The method of Claim 531 wherein n is 0-5.

545. (Previously presented) The method of Claim 544 wherein n is 0.

546. (Previously presented) The method of Claim 531 wherein P₂ comprises a metal-binding sequence.

547. (Previously presented) The method of Claim 546 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein:

m is 0-5; and

Xaa₅ is an amino acid having a free side-chain -NH₂, and (Xaa₄)_m, if present, or P₁ is attached to Xaa₅ by means of the side-chain amino group.

548. (Previously presented) The method of Claim 547 wherein Xaa₅ is Orn or Lys.

549. (Canceled)

550. (Previously presented) The method of Claim 546 wherein P₂ comprises a sequence which binds Cu(I).

551. (Previously presented) The method of Claim 550 wherein P₂ comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys,

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Cys Xaa₄ Cys,
Cys Xaa₄ Xaa₄ Cys,
Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
γ-Glu Cys Gly.

552. (Previously presented) The method of Claim 551 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

553. (Previously presented) The method of Claim 531 wherein P₂ comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

554. (Previously presented) The method of Claim 553 wherein P₂ is hydrophobic or an arginine oligomer.

555. (Previously presented) The method of Claim 531 wherein at least one of the amino acids of P₁ other than β-alanine, when present, is a D-amino acid.

556-557 (Canceled)

558. (Previously presented) The method of Claim 531 or 555 wherein at least one of the amino acids of P₂ is a D-amino acid.

559. (Currently amended) A method of treating an angiogenic disease or condition in an animal comprising administering to the animal an amount of a metal-binding peptide which does not have a metal ion bound to it or of a physiologically-acceptable salt of the peptide, the amount of the peptide or salt which is administered to the animal being effective to inhibit angiogenesis, the sequence of the peptide being:

_____ P₁ - P₂,_____

wherein:

_____ P₁ is:_____

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Xaa₁ Xaa₂ His or

Xaa₁ Xaa₂ His Xaa₃,

the P₁ portion of the peptide being linear:

P₂ is (Xaa₄)_n;

Xaa₁ is the N-terminal amino acid of the peptide, the only substituents on the α -amino group of Xaa₁ are hydrogen, and Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

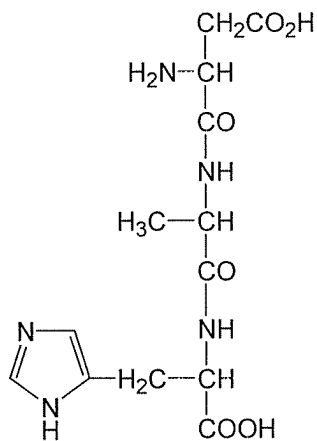
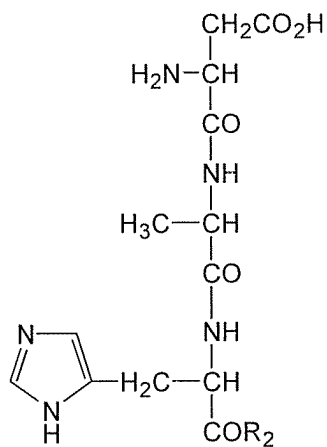
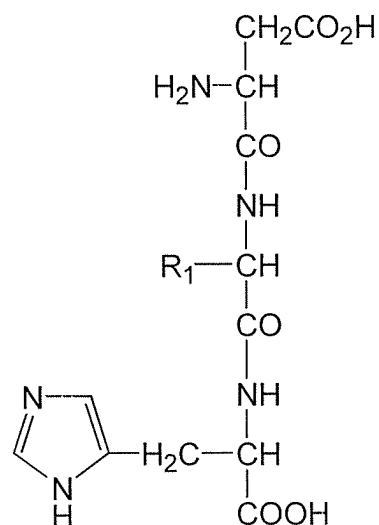
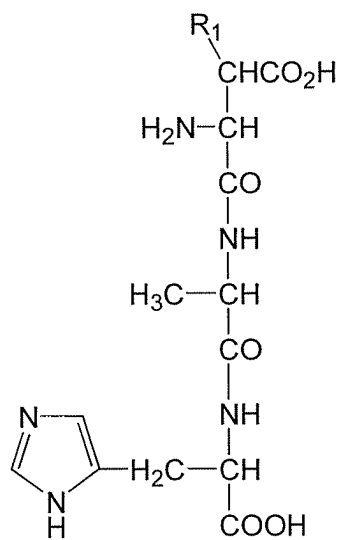
Xaa₄ is any amino acid;

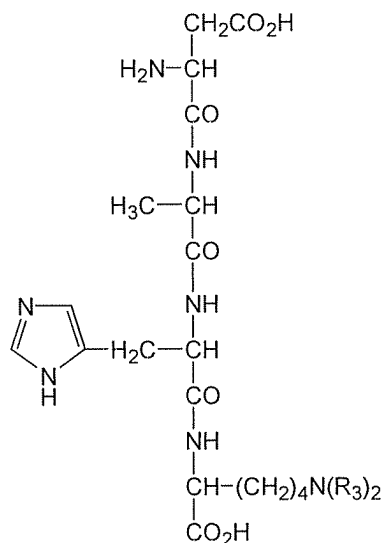
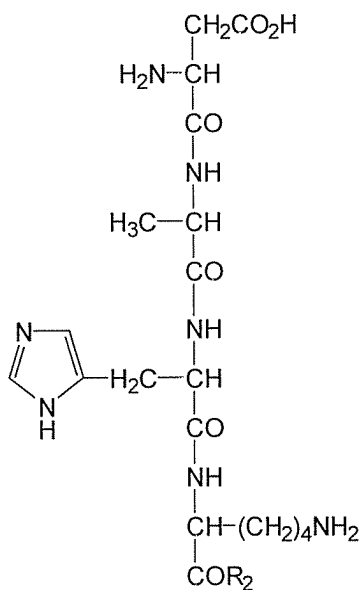
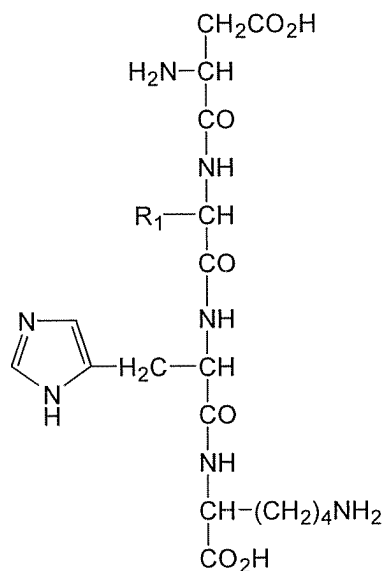
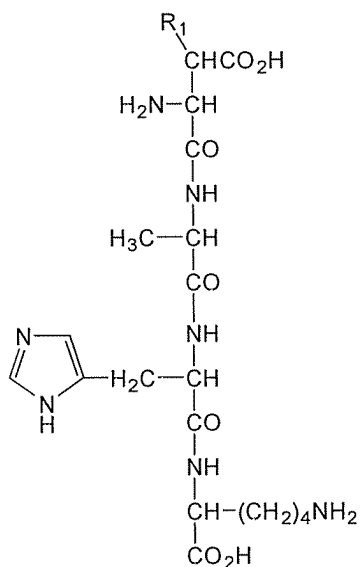
n is 0-10; and

~~The method of Claim 531 wherein~~ at least one amino acid of P₁ or at least one amino acid of P₂, or at least one amino acid of P₁ and at least one amino acid of P₂ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

560. (Previously presented) The method of Claim 559 wherein the terminal -COOH of P₁-P₂ is substituted to produce -COR₂, wherein R₂ is -NH₂, -NHR₁, -N(R₁)₂, -OR₁, or -R₁, wherein R₁ is an alkyl, aryl or heteroaryl.

561. (Previously presented) The method of Claim 559 wherein n is 0 and P₁ has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $-N(R_1)_2$, $-OR_1$, or $-R_1$; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together

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form a non-peptide, metal-binding functional group.

562. (Previously presented) The method of Claim 561 wherein R_2 is $-NH_2$.

563. (Currently amended) The method of Claim 531 wherein the method further comprises administering an effective amount of a second ~~another~~ metal-binding compound in combination with the P₁-P₂ peptide.

564. (Currently amended) The method of Claim 563 wherein the second metal-binding compound binds iron.

565. (Previously presented) The method of Claim 564 wherein the iron-binding compound is deferoxamine mesylate.

566. (Currently amended) The method of Claim 563 wherein the second metal-binding compound binds Cu(I).

567. (Previously presented) The method of Claim 566 wherein the Cu(I)-binding compound is a peptide.

568. (Previously presented) The method of Claim 567 wherein the Cu(I)-binding peptide comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys

Cys Xaa₄ Cys,

Cys Xaa₄ Xaa₄ Cys,

Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,

Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],

Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],

Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or

γ -Glu Cys Gly,

wherein Xaa₄ is any amino acid.

569. (Currently amended) The method of any one of Claims 531-542, 544-548, ~~or 550-~~

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~~568~~ 550-555, 558-568 or 577-580 wherein the angiogenic disease or condition is a neoplastic disease, a connective tissue disorder, psoriasis, an ocular angiogenic disease, a cardiovascular disease, a cerebral vascular disease, hemophiliac joints, an immune disorder, a benign tumor, hypertrophy, endometriosis, polyposis, or obesity.

570. (Previously presented) The method of Claim 569 wherein the angiogenic disease or condition is a neoplastic disease.

571. (Previously presented) The method of Claim 570 wherein the neoplastic disease is a tumor.

572. (Previously presented) The method of Claim 571 wherein the tumor is located in the bladder, brain, breast, kidney, liver, pancreas, lung, cervix, ovary, prostate, stomach, intestines, colon, rectum, or uterus.

573. (Previously presented) The method of Claim 570 wherein the neoplastic disease is tumor metastasis.

574. (Previously presented) The method of Claim 569 wherein the angiogenic disease or condition is psoriasis.

575. (Previously presented) The method of Claim 569 wherein the angiogenic disease or condition is an ocular angiogenic disease.

576. (Previously presented) The method of Claim 575 wherein the ocular angiogenic disease is macular degeneration.

577. (New) A method of treating an angiogenic disease or condition in an animal comprising administering to the animal an amount of a metal-binding peptide which does not have a metal ion bound to it or of a physiologically-acceptable salt of the peptide, the amount of the peptide or salt which is administered to the animal being effective to inhibit angiogenesis, the sequence of the peptide being:

Xaa₁ Xaa₂ His

wherein:

Xaa₁ is the N-terminal amino acid of the peptide, the only substituents on the α -amino

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group of Xaa₁ are hydrogen, and Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine.

578. (New) The method of Claim 577 wherein:

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, phenylalanine, cysteine or α -hydroxymethylserine; and

Xaa₂ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, asparagine, glutamine, lysine, hydroxylysine, histidine, arginine, cysteine, methionine, or α -hydroxymethylserine.

579. (New) The method of Claim 577 wherein:

Xaa₁ is serine, threonine or α -hydroxymethylserine; and

Xaa₂ is glycine, alanine, valine, leucine, isoleucine, serine, threonine or α -hydroxymethylserine.

580. (New) The method of Claim 577 wherein at least one of the amino acids of the peptide other than β -alanine, when present, is a D-amino acid.